Abstract# 432 **Poster Board#/Session: 432-I**

RITUXIMAB THERAPY IN HEMATOLOGIC MALIGNANCY PATIENTS WITH CIRCULATING BLOOD TUMOR CELLS: ASSOCIATION WITH INCREASED INFUSION-RELATED SIDE EFFECTS AND RAPID TUMOR LYSIS. J.C. Byrd, J.K. Waselenko, T.A. Maneatis*, T. Murphy, R. Weickum*, F.T. Ward, C.A. White. *Walter Reed Army Medical Center, Washington D.C. Brook Army Medical Center, San Antonio TX, and IDEC Pharmaceuticals Corp, San Diego CA, USA.*

Rituximab was recently approved for use in relapsed and previously treated low-grade non-Hodgkin's lymphoma (NHL), however little data exist regarding the safety of this agent in patients with hematologic malignancies possessing a high number of tumor cells in the blood. We describe our preliminary experience with two such patients in whom we noted rapid reduction of blood tumor cells which was associated with severe pulmonary infusion-related toxicity and thrombocytopenia. Two additional patients were collected from physician submitted reports of adverse events related to rituximab treatment. Pre-treatment characterization of these patients included a median age was 60 years (range 26-73) with the diagnosis of B-prolymphocytic leukemia (B-PLL) [n = 2], chronic lymphocytic leukemia (CLL) [n = 1] or transformed non-Hodgkin's lymphoma [n = 1]. All of these patients had elevated leukocyte counts as a consequence of blood tumor involvement, bulky adenopathy and organomegaly. All 4 patients developed a unique syndrome of severe infusion-related reactions characterized by fever (n = 4), rigors (n = 4), bronchospasm with associated hypoxemia (n = 3) requiring temporary cessation of rituximab therapy. Concurrent with these symptoms, a rapid decrement in circulating tumor cell load (mean pre-treatment 98 $\times 10^9$/L; range 73-132 vs. mean post-treatment 11 $\times 10^9$/L; range 3.7-24.6) with mild laboratory evidence of rapid tumor lysis. Thrombocytopenia, a finding not commonly associated with rituximab therapy was noted in all four patients (mean pre-treatment 145 $\times 10^9$/L; range 57-277 vs. mean post-treatment 56 $\times 10^9$/L; range 2-120), requiring transfusion in one case. Symptoms of this syndrome required hospitalization but resolved with supportive care. Subsequent rituximab treatments were well tolerated in all patients. Two subsequent patients with CLL have been treated at our institution with high blood tumor counts utilizing stepped up dosing (100 mg on day 1 followed by completion of the remaining therapy on day 2) with demonstrated efficacy, thombocytopenia but minimal infusion-related toxicity. Rituximab administration in patients with hematologic malignancies who have blood tumor cell involvement may be associated with a higher frequency of severe initial infusion-related reactions and thrombocytopenia mandating careful clinical monitoring. Given the preliminary activity of rituximab in these patients, future studies in CLL and PLL possibly utilizing a stepped up dosing schedule appears warranted.

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Abstract# 433 **Poster Board#/Session: 433-I**

RITUXIMAB THERAPY IN PREVIOUSLY TREATED WALDENSTROM'S MACROGLOBULINEMIA: PRELIMINARY EFFICACY AND ACTIVITY. J.C. Byrd, C.A. White, B. Link, S. Thomas*, W.S. Velasquez, J. Rosenberg*, A.J. Grillo-Lopez. *Walter Reed Army Medical Center, Washington D.C.; IDEC Pharmaceuticals Corp., San Diego CA; University of Iowa, Iowa City IA; University of Texas at Galveston, Galveston TX, USA.*

Waldenstroms macroglobulinemia (WM) is a rare low-grade lymphoproliferative disorder for which few therapies are effective. Although patients (pts) with WM often are reported with cases of small lymphocytic lymphoma, this disease has characteristic lymphoplasmacytic histology, bright CD20 expression, and IgM paraproteinemia. Rituximab is a chimeric anti-CD20 monoclonal antibody that produces a 50% response rate in previously-treated low-grade lymphoma, but has no previously described efficacy in the WM subtype. We report 7 pts with WM treated (Rx) on clinical trials performed by IDEC pharmaceuticals (n = 6) or at our institution (n = 1). Characteristics of these pts included a median age of 60 years (range 50-75) with 5 being female. All patients were symptomatic with a median performance status of 1 (range 1-3) with all having measurable disease independent of paraproteinemia. Pts were heavily pre-rx, having received a median of 3 (range 1-4) prior rx for their WM. Prior rx had included alkylator therapy in all patients (5 refractory) and fludarabine in four (all refractory) with 5 being refractory to their last therapy. Pre-rx laboratory features included a mean serum IgM of 2.9 g/dl (range 0.72-6.28), leukocyte count 5.1/cm^3 (range 3.0-6.6), hemoglobin 10.5 g/dl (range 8.6-13.4), and platelets 219/cm^3 (range 32-332). All patients received Rituximab (375 mg/m^2) weekly for 4 (n = 6) or 8 (n = 1) weeks. Therapy was tolerated well with 5 pts having infusion-related toxicity (4 grade 1/1 grade 3) during the first rx. Cellular immune function as measured by Mean CD4 (pre-Rx 344/mm^3 vs. 3 months post-Rx 331/mm^3; p = 0.89) and CD8 (pre-Rx 608/m^3 vs. 3 months post Rx 654/mm^3; p = 0.32) lymphocyte counts were not significantly altered by rituximab therapy. Corresponding with this was the absence of opportunistic infections and only one post-therapy grade 3 bacterial sinusitis. Responses as assessed by at least 50% reduction in all measurable disease (NHL partial response) occurred in 4 (57%) of pts, while 50% reduction in paraproteinemia (WM partial response) was noted in 3 (43%) of these same pts. The median progression-free survival for these 7 pts was 8 months (range 3-27+ months). These preliminary data suggest that rituximab has clinical activity in pre-treated Waldenstrom's macroglobulinemia without decrements in hematologic or cellular immune parameters that are commonly noted with other therapies employed in this disease. Based upon these data, future studies utilizing rituximab in both previously treated and untreated Waldenstrom's macroglobulinemia appear warranted.

Abstract# 434 **Poster Board#/Session: 434-I**

EFFECTS OF INTRAVENOUS IBANDRONATE THERAPY ON SKELETAL RELATED EVENTS (SRE) AND SURVIVAL IN PATIENTS WITH ADVANCED MULTIPLE MYELOMA. A. Fontana*, Z. Herrmann*, H.D. Menssen*, A. Sezikalova*, C. Boewer*, T. Facon*, M.R. Lichtinitser*, C.R.J. Singer*, L. Fuller*, C. Ziegler*, M. Wetterwald*, D. Fiere, T. Rockett, D. Thiel, P. Garnero*, P.D. Delmas*. *For the Myeloma Ibandronate Study Group, Hospital Edouard Herriot, Lyon, France; Roche/Boehringer Mannheim, Mannheim; Benjamin Franklin Hospital, Berlin; Institute for Hematology and Blood Transfusion, Bratislava, Slovakia; St. Hedwigs-Krankenhaus, Berlin, Germany; C.H.R., Claude Huriez, Lille, France, Cancer Research Center, Moscow, Russia; Royal United Hospital, Bath, UK.*

The median survival of patients with advanced multiple myeloma is still poor despite the improvement of chemotherapy regimens. Treatment with bisphosphonates holds the promise to improve skeletal morbidity and may be survival. We conducted a multicenter double-blind, randomized, placebo-controlled trial to investigate the efficacy and safety of the aminobisphosphonate ibandronate (Bondronat®) to prevent skeletal related events (SRE; peripheral pathologic fracture, vertebra height reduction, hypercalcemia, severe bone pain requiring opiates, radiotherapy to bone, surgery to bone) in patients with multiple myeloma stage II or III. In addition, markers of bone turnover were analyzed every three months during the first 6 months and then every 6 months. From 214 randomized patients, 198 patients received ibandronate as a monthly intravenous bolus injection or placebo in addition to standard chemotherapy. 99 patients per group were evaluable for efficacy (intent to treat analysis, median time in study 17 months). No significant difference in the overall evaluation of SRE/year was noted between both study groups (placebo: 2.05 vs ibandronate: 2.13). However, 58% of patients in the ibandronate group showed a sustained reduction in bone resorption assessed by three markers of bone turnover. Those "responding" patients had a significant reduction in SRE/year (1.14 vs 2.4, p = 0.02). Survival was also recorded after the end of the double-blind treatment period for up to 50 months (median = 30 months). There was a trend for an improvement of the median survival with ibandronate (33 vs 28 months with placebo, n.s.). In addition, 61 patients with WHO stage 2-4 survived in median 10.4 months longer on ibandronate compared to placebo (25 vs 14.6 months, n.s.). Ibandronate was safe and well tolerated during up to 24 cycles of therapy. In conclusion, although monthly injection of 2 mg ibandronate did not decrease the incidence of new SRE in the overall population, treatment was effective in a subgroup of "responder" patients identified by urinary crosslaps, osteocalcin and bone alkaline phosphatase measurements. Patients not adequately responding to 2 mg ibandronate probably require higher dosage of this bisphosphonate. Finally, a trend for improved survival with ibandronate was observed and requires further investigation.

Abstract# 435 **Poster Board#/Session: 435-I**

PAMIDRONATE INHIBITS GROWTH OF MYELOMA IN VIVO IN THE SCID-hu SYSTEM. S. Yaccoby, B. Barlogie, J. Epstein. *Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR, USA.*

Bisphosphonates are widely used in patients with myeloma and other malignancies to prevent bone manifestations. It appears that in myeloma patients, like in patients with breast cancer, the bisphosphonates effect tumor growth. We used the SCID-hu model for human myeloma (Yaccoby, Blood 1998, in press) to evaluate the anti-myeloma effects of pamidronate. Bone marrow cells from patients with myeloma were injected into SCID-hu hosts. IRB-approved consent forms are on record. When myeloma was established, as determined by human Ig levels of 300 mg/ml, the mice were treated with bi-weekly sub cutaneous injections of 90 mg/Kg freshly prepared pamidronate. Tumor growth was followed by hIg levels, bone resorption radiologically. Osteoclasts were identified by TRAP staining and the extent of myeloma growth by clg immunohistochemistry and by flow cytometry. Myeloma growth was restricted to the human bones, and was associated with severe bone resorption that was readily visible on X-radiograms. Both hIg levels and extent of bone resorption continued to increase in untreated mice. In contrast, pamidronate treated hosts had no further loss of bone density. In these mice tumor growth was inhibited by 40-86% compared with controls, and the numbers of apoptotic myeloma cells increased markedly. The Myeloma bearing hosts had increased numbers of osteoclasts that was not reduced by pamidronate (9 ± 1, 32 ± 3, and 27 ± 4 osteoclasts/mm^2 in control, untreated, and treated mice, respectively). Myeloma bearing mice also showed loss of bone density and increased osteoclast numbers in the femurs, without bone marrow involvement. Pamidronate prevented bone loss in the murine bone as well, and like in the human bone, had no effect on the number of osteoclasts. The osteoclasts in the human and murine bones of treated mice were larger in size and appeared inactive. We conclude that pamidronate has an anti-myeloma effect *in vivo*. Whether the drug affects myeloma cells directly or indirectly by interfering with elements of the supportive bone marrow environment needs to be studied.

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